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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,110	04/12/2001	Pankaj J. Pasricha	265.0009 0101	5306

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,110	PASRICHA ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-27 and 31-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-27 and 31-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 28, 2003 has been entered.

DETAILED ACTION

This application filed April 12, 2001, claims benefit to provisional applications 60/198,806, filed May 13, 2000, and 60/232,301, filed September 12, 2000.

As indicated in Applicants' request for continued examination, the amendment filed July 25, 2003, has been entered. Claims 18-20 and 28-30 have canceled. Claims 21, 26, 31, 32, 34, 35, 38, 41 have been amended. Claims 44 and 45 have been added. Claims 21-27, 31-45 are pending.

Election/Restriction

As stated in the previous office action Groups I and II were rejoined because both groups could be examined without serious burden as they are drawn to a method for the treatment of the elected species of a degenerative disorder. Further, the election of species was maintained

because the search and specific considerations for each disorder would not be co-extensive, and would constitute an undue burden.

Newly added claims 44 and 45 recited specific disorders associated with the gastrointestinal systems and will be examined to the extent they encompass the elected invention of a method for the treatment of a degenerative disorder.

In the instant amendment Applicants summarize the restriction requirement and indicate that all the claims encompass practicing the same method steps, and request clarification of the claim summary provided in the final office action. Further, Applicants request clarification of the election of species because it appears that the examination (for example the 102(b) rejection) is inconsistent with election. See Applicants amendment pages 5-8. Applicants' arguments and request is noted.

The summary of the claims was for clarity of record. With respect to the consistency of the rejections of record and the elected species, it is noted that the specification broadly defines the alimentary tract to include organs such as the liver and thus are consistent with the teaching of Lou *et al*. Further, the claims include both open language and broad terms encompassing progeny of stem cells in any context, including the intact organ that arose from such cells. The claims have been given the broadest reasonable interpretation in light of the art and teaching in the present specification. The art rejections have been made to be consistent with the breadth of the invention as presently claimed, as will be discussed in greater detail below.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 21-27, 31-45 are currently under examination as they are drawn to the elected invention of a method for the treatment of a degenerative disorder.

Claim Objections

Claims 21-27, 31-45 are objected to because of the following informalities:

The election of species was made to a *degenerative* disorder, however the claims broadly encompass any gastrointestinal alimentary tract disorder. The claims should be amended to reflect the elected invention.

Applicants note that MPEP 809.02(a) states that claims will be limited to a single species if no generic claim is found allowable and that it is inappropriate at this time to require amendment to the claims.

As indicated in the prior office action, claims 21-43 are broader than the claims previously set forth as they are drawn to treatment of a degenerative disorder. No generic claim has been found allowable, accordingly the claims should be amended to reflect the elected

invention. Again, as noted in the section of Election/Restriction, claims 21-43 are broader and different than the methods previously set forth in group I, original claims 1-17, and should be amended to reflect the elected invention.

Claim Rejections - 35 USC § 112

Claim 37 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Upon review of Applicants' comments (see page 10 of Applicants' amendment) and supporting portions of the specification, Examiner agrees that the specification supports 'substance P' as recited in the claims.

Claims 21-27, 31-43 stand rejected and new added claims 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants summarize the teaching of the instant specification and the examples provided in the disclosure as well as those in the declaration of Dr. Pasricha and Micci (submitted with prior amendment)(pages 10-11) Summarizing the rejection set forth by the office Applicants

argue that the basis of the rejection is moot in light of the claim amendments given the guidance and evidence of the working examples provided in the instant specification. See Applicants' amendment, pages 10-13. Applicants' arguments have been fully considered but not found persuasive.

Initially, Examiner acknowledges the reduction to practice the direct injection of cells into the pylorus of a mouse, and that the cells injected therein can be detected by the presences of NOS production. However, this is insufficient to demonstrate that the NOS produced is demonstrative of treatment or that the cells would produce an affect once transplanted. The claims are very broad encompassing the treatment of any gastrointestinal disorder, and the specification teaches that gastrointestinal disorders are complex relying on the balance of many factors. The example where a knockout mouse only missing the NOS gene is treated by replacing NOS production is not found to be supportive of a model of the specific disorders taught and claimed in light of the complexity of the disorders. The basis of the instantly claimed invention appears to focus on the fact that neuronal cells have a certain plasticity and can be transplanted to areas other than the brain. However, while such cells may be able to be transplanted and grow in other tissues of an animal, this insufficient evidence that they will be capable of treating a disorder. Again, the specific disorders taught in the instant specification are complex and presently not subject to simple or conventional treatments recognized in the art. Simply providing a cell to an area affected or affecting a disorder is insufficient to provide a

treatment. Further, there is no evidence that the specific disorders listed are a consequence of a degenerative disorder as elected and currently under examination.

As indicated in the final office action, the specification recites only general methodology and provides no means to avoid the hosts immune system which is the major source for graft rejection in xenotransplantation and applies to all the claims. Applicants arguments that neuronal cells have been transplanted in the brain are not found persuasive because the brain is immonoprivaledged and not be subject to the same surveillance that the present invention would be subject. Again, as acknowledged by Applicants, the evidence provided in the declaration does not address the problems of xenotransplantation in that cells for transplantation are isolated from a mouse and returned to a mouse, and the issue of cross species transplantation is not addressed. As set forth in the previous office action, Mandel teaches that conventional methods known in the art are not the "usually adequate for control of allograft rejection generally does not prevent xenograft rejection" (page 155; abstract). Applicants' arguments that the evidence provided in the declaration address the issue of xenotransplantation is not convincing because relevant evidence is not presented. Further, the present specification only provides general guidance for avoiding graft rejection relying on the art for the specific guidance to affect immunosuppression, therefore the disclosure is subject the same limitations recognized in the art. The specification provides several disorders associated with the gastrointestinal tract of a subject, however there is no nexus that neuronal stem cells would replace these cells. Further, in general and with respect to the specific disorders set forth in claim 27, there is no indication that providing a neuronal cell

will provide any form of treatment to a subject. It is maintained that the present specification fails to provide the necessary guidance to practice the invention wherein cells from different species are used. The specification provides no specific guidance to overcome this art recognized limitation for the transplantation of cells to the pancreas.

In addition, as set forth previously stem cells isolated from different tissues provide a unique cell with different inherent properties. Examiner acknowledges that the art has taught that pancreatic and liver stem cells have been isolated, however there is no nexus between the property demonstrated with these cells and the properties of neuronal stem cells disclosed in the instant specification. The evidence presented in the specification and the declaration provide no basis that neuronal cells have the capacity to differentiate into cells which produce insulin. Further, even if the neuronal cells were demonstrated to have the capacity to differentiate into beta cells, there is evidence that they would behave any differently that endogenous beta cells in the subject. More specifically, by providing a cell to subject which differentiates into a cell which produces insulin, one would expect the cell to be regulated like an endogenous cell and produce insulin as required in the subject, and there would be no 'enhanced levels of insulin' only a normal level of regulated insulin production. There is no guidance for providing cells to a normal subject who maintain a normal number of cells.

The specification is silent with respect to specific guidance to the number of neuronal stem cells to transplant which could then differentiate and subsequently provide any therapeutic affect. Examiner notes evidence provided in Exhibit D of the declaration and that these experiments demonstrate that providing NOS can alleviate symptoms caused by the lack of NOS, however the specification is silent with respect to degenerative disorders in which lack of NOS is cause of the disorder or would be ameliorated by its administration. Further, it is noted that the evidence indicates that substance P is secreted by the differentiated neuronal stem cells *in vitro*, however even if this differentiation was recapitulated *in vivo* the specification is silent to why or how the artisan would use this observation.

As noted in the previous office action the claims are drawn broadly to a method of treating a degenerative disorder comprising implanting stem cells or progeny thereof into a gastrointestinal organ. The specification teaches that degenerative disorders is considered broadly to encompass specific diseases associated with the gastrointestinal tract as well as a variety of disorders not traditionally considered gastrointestinal disorders but related to organs associated with the gastrointestinal organs (page 5; lines 15-27). Encompassed within this broad definition diseases such as diabetes, cirrhosis of the liver, as well as other diseases which are associated with the destruction of a particular organ could be treated by the instantly claimed methods. It is noted that the methods simply recite implanting stem cells into a subject, though dependent claims recite specific routes of delivery and delivery to particular organs. The specification provides no working example of the instantly claimed invention as it is drawn to

providing treatment or the production of insulin. The only working example presented in the disclosure describes the isolation of a neural stem cell from fetal tissue and transplantation of said cells into the pylorus of the gastrointestinal tract of a mouse. In the working example the neuronal cells differentiate into nitrigenic neurons (page 14). The specification provides only a general summary of a broad range of potential disorders to be treated and a description of sources of stem cells known in the art at the time of filing.

The teaching in the specification for transplantation is noted however the few lines of guidance and the working example is insufficient teaching for the scope of transplantation encompassed by the instant claims. Examiner would concede that transplanting neuronal stem cells form fetal tissues into the brain has been done, however this methodology is not applicable for other tissues. The specification is silent with respect to specific methodology for cell transplantation and provides no guidance for specific treatments of specific disorders except to for the general administration of stem cells for affecting any desired treatment. Moreover, the means to determine appropriate sites in the tissues encompassed by the claims is not adequately set forth. There is no teaching for specific delivery methods for all the tissues encompassed by the claimed method or the amounts of cells to be delivered that one would expect to affect treatment. As discussed above the specification fails to provide a reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application (27 USPQ2d 1662 *Ex parte Maizel)*. Further, the specification fails to provide the necessary guidance to overcome even the specific art recognized limitations for providing

cells which produce insulin. The breadth of the claims is large encompassing any type of stem cell, any means of delivery and affecting treatment for any type of disorder. In view of the quantity of experimentation necessary to determine the parameters listed above for each disorder and/or cell type, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to affect any treatment, and the general unpredictable state of the art with respect to affecting any treatment, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed. The specification provides insufficient guidance to teach how to engineer the delivery of insulin to any therapeutic effect in any of the methods proposed.

The high degree of unpredictability associated with a single claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific methodology to practice the full breadth of the claimed invention. In the instant case, the specification does not provide any specific guidance for any specific disease for a therapeutic benefit by a cell based therapy. Further, the specification fails to provide any correlation between routes of delivery (e.g. intratumoral, intravenous etc.), implantation into cells, dosage amounts/frequencies, and specific forms of diseases treatable by the cells comprising such as those disclosed in the instant specification. Without such guidance in the specification the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan. (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005).

Therefore, it is maintained that in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed, and the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Upon review of the specification noted by Applicants, Examiner agrees that 'administering the cells locally' is clearly defined. While it can be maintained that the specification does not specifically define the methods encompassed by local delivery of cells, and it is unclear if the term refers to delivery of cells to where the cells are lacking and need to be repopulated, this is not the basis of a rejection made under 35 USC 112, second paragraph, rather this is an issue of enablement that should be made under 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 22, 28, 29, 32 stand rejected under 35 U.S.C. 102(b) as being anticipated by Luo *et al.* (Xenotransplantation 1998 Aug;5(3):197-206).

Applicants argue the Luo *et al.* does not teach that implantation of stem cells or progeny thereof, nor that the method should be done in a subject suffering from a gastrointestinal disorder, and thus does not anticipate the claims. See bottom of page 14. Applicants' arguments have been fully considered but not found persuasive.

As indicated in the previous office action claim 21 broadly is drawn to a method of repopulating tissues with a gastrointestinal organ comprising implanting stem cells or progeny thereof into the gastrointestinal organ. There is no limitation on the nature of progeny or how the cells are provided, and thus claims 21, 22, 28, 29, 32 broadly encompasses transplanting a tissue. Furthermore, claims 28 and 29 indicate that the solid gastrointestinal organ can be the liver. At the time of filing, Luo *et al.* teach a method of liver transplantation. By providing liver cells in the method Luo *et al.* teach a method of repopulating cells of a gastrointestinal organ. Applicants' arguments are not found persuasive because the claims clearly set forth limitations taught by Luo *et al.*

Claims 21, 22, 25, 26, 30, 31, 32 stand rejected under 35 U.S.C. 102(b) as being anticipated by Keller *et al.* (J Invest Surg 1997 Nov-Dec;10(6):375-8).

Applicants argue the Luo *et al.* does not teach that implantation of stem cells or progeny thereof, nor that the method should be done in a subject suffering from a gastrointestinal disorder, and thus does not anticipate the claims. See bottom of page 14. Applicants' arguments have been fully considered but not found persuasive.

As indicated in the previous office action claim 21 broadly is drawn to a method of repopulating tissues with a gastrointestinal organ comprising implanting stem cells or progeny thereof into the gastrointestinal organ. There is no limitation on the nature of progeny or how the cells are provided, and thus claims 21, 22, 25, 26, 30, 31, 32 broadly encompasses transplanting a tissue. Further, claims 28 and 29 indicate that the hollow gastrointestinal organ can be the bowel or intestine. At the time of filing, Keller *et al.* teach a method of intestine transplantation. By providing the intestine to a subject in the method Keller *et al.* teach a method of repopulating cells of a gastrointestinal organ. Applicants' arguments are not found persuasive because the claims clearly set forth limitations taught by Keller *et al.*

Conclusion

No claim is allowed.

Claims 21, 22, 25, 26, 28, 29, 30, 31, 32 are anticipated by the art of record. The remaining claims are free of the art of record because the art fails to teach and enable the breadth of the instantly claimed method. However, the claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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